AMENDMENTS TO THE SPECIFICATION UNDER 37 C.F.R. § 1.121(b)(1)

1. Please amend the paragraph after the heading CROSS REFERENCE TO RELATED APPLICATIONS as follows:

This application is a divisional application of U.S. Patent Application Ser. No. 09/640,363, filed August 16, 2000, which claims priority to U.S. Provisional Application Serial Nos. 60/149,115, filed August 16, ~~1999,~~1999; 60/172,452, filed December 17, 1999; 60/176,570, filed January 18, 2000; and 60/194,534, filed April 4, 2000.

2. Please amend the paragraphs beginning on page 8, line 4 and ending on line 14, as follows:

Active site I:
35 AA's ~~upstream~~downstream from N-terminus: STTK (SEQ ID NO:1)

Active site II:
57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif: SGC, SGN, or SAN

Active site III:
111 AA's ~~upstream~~downstream from SGC motif: KTG

Active site IV:
41 AA's ~~upstream~~downstream from SGC motif: ENKD (SEQ ID NO:2)

3. Please amend the paragraphs beginning on page 8, line 30 and continuing through page 9, line 8, as follows:

Active site I:
PBP: 35 AA's ~~upstream~~downsteam from N-terminus: STTK (SEQ ID NO:1)
NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

Active site II:
PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif: SGC, SGN, or SAN
NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

Active site III:
PBP: 111 AA's ~~upstream~~downstream from SGC motif: KTG

Active site III:
PBP: 111 AA's ~~upstream~~downstream from SGC motif: KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG

Active site IV:
PBP: 41 AA's ~~upstream~~downstream from SGC motif: ENKD (SEQ ID NO:2)
NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)

4. Please amend the paragraphs on beginning on page 9, line 34 and continuing through page 13, line 2, as follows:

Active site I:
PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)
NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)
>dbj|AP001769: NSRK (SEQ ID NO:5)

Active site II:
PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1)
motif:..... SGC, SGN, or SAN
NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3)
motif: SFG
>dbj|AP001769: SFG

Active site III:
PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG
>dbj|AP001769: KLG

Active site IV:
PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)
NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)
>dbj|AP001769: ERSI (SEQ ID NO:6)
2) >dbj|AP000827.2|AP000827 Homo sapiens chromosome 11 clone RP.

Active site I:
PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)
NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)
>dbj|AP000827.2: NSRK (SEQ ID NO:5)

Active site II:

PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1)
motif:..... SGC, SGN, or SAN
NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3)
motif: SFG
>dbj|AP000827.2: SFG

Active site III:
PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG
>dbj|AP000827.2: KLG

Active site IV:
PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)
NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)
>dbj|AP000827.2: ERSI (SEQ ID NO:6)
3) >dbj|AP000648.2|AP000648 Homo sapiens chromosome 11 clone CM.

Active site I:
PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)
NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)
>>dbj|AP000648.2: NSRK (SEQ ID NO:5)

Active site II:
PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1)
motif:..... SGC, SGN, or SAN
NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3)
motif: SFG
>dbj|AP000648.2: SFG

Active site III:
PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG
>dbj|AP000648.2: KLG

Active site IV:
PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)
NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)
>dbj|AP000648.2: ERSI (SEQ ID NO:6)
4)> gb|AC074003.2|AC074003 Homo sapiens chromosome 2 clone RP11.

Active site I:

PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)

NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

gb|AC074003.2|AC074003: STQ-

Active site II:

PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif:..... SGC, SGN, or SAN

NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

gb|AC074003.2|AC074003: SFG

Active site III:

PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG

NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG

gb|AC074003.2|AC074003: KLG

Active site IV:

PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)

NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)

gb|AC074003.2|AC074003 ER GV

5)> emb|AL162372.6|AL162372 Homo sapiens chromosome 13 clone RP.

Active site I:

PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)

NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

emb|AL162372.6: STQ-

Active site II:

PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif:..... SGC, SGN, or SAN

NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

emb|AL162372.6: SFG

Active site III:

PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG

NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG

emb|AL162372.6: KLG

Active site IV:

PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)

NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)

emb|AL162372.6 ER GV

6) gb|AC024234.5|AC024234 Homo sapiens chromosome 11 clone RP1.

Active site I:

PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)

NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

gb|AC024234.5|AC024234: STQ-

Active site II:

PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif:..... SGC, SGN, or SAN

NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

gb|AC024234.5|AC024234: SFG

Active site III:

PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG

NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG

gb|AC024234.5|AC024234: KLG

Active site IV:

PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)

NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)

gb|AC024234.5|AC024234 ER GV

7) dbj|AP002369.1|AP002369 Homo sapiens chromosome 11 clone RP....

Active site I:

PBP: 35 AA's ~~upstream~~downstream from N-terminus:..... STTK (SEQ ID NO:1)

NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

dbj|AP002369.1: STQ-

Active site II:

PBP: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif:..... SGC, SGN, or SAN

NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

dbj|AP002369.1: SFG

Active site III:

PBP:111 AA's ~~upstream~~downstream from SGC motif:..... KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG
dbj|AP002369.1: KLG

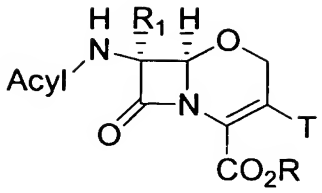
Active site IV:
PBP:41 AA's ~~upstream~~downstream from SGC motif:..... ENKD (SEQ ID NO:2)
NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)
dbj|AP002369.1 ER GV

5. Please amend the paragraphs beginning on page 14, line 5 and ending on line 21, as follows:

Enhanced concentrations of drug substances, including NAALADase inhibitors in the brain, can also be achieved by co-administration with P-glycoprotein efflux inhibitors such as those described in U.S. Patent Numbers 5,889,007; 5,874,434; 5,654,304; 5,620,855; 5,643,909; and 5,591,715, the specifications of which patents are expressly incorporated herein by reference. Alternatively, β-lactam ~~β-lactams~~ antibiotic compounds useful in accordance with this invention, including penicillins, cephalosporins, penems, 1-oxa-1-dethia cephems, clavams, clavems, azetidinones, carbapenams, carbapenems, and carbacephems, can be administered alone or in combination with art-recognized β-lactamase inhibitors, which themselves may or may not be β-lactam compounds or compounds capable of exhibiting selective affinity for penicillin-binding proteins. Examples of β-lactamase inhibitors which can be used alone or in combination with other neuropeptidase inhibitors useful in accordance with this invention for treatment and/or prevention of cognitive or behavioral disorders are other β-lactam compounds which may or may not exhibit independent clinically significant antibacterial activity, such as clavulanic acid and thienamycin and analogs thereof, sulbactam, tazobactam, sultamicillin, and aztreonam and other monolactams.

6. Please amend the paragraphs beginning on page 34, line 22 and ending on page 35, line 4, as follows:

In one preferred embodiment of the present invention the protease inhibitor is a compound of the formula:



wherein R is hydrogen, a salt forming group or an active ester forming group; R^1 is hydrogen or C_1-C_4 alkoxy; T is C_1-C_4 alkyl, halo (including ~~chlori, fluro, biomo~~chloro, fluoro, bromo, and iodo), hydroxy, O(C_1-C_4)alkyl, or -CH_2B wherein B is the residue of a nucleophile B:H, and ~~acyl~~ Acyl is the residue of an organic acid ~~Acyl OH~~Acyl-OH.

7. Please amend the paragraphs beginning on page 36, line 5 and ending on line 18, as follows:

Suitable pharmaceutically acceptable salts of the carboxy group of the above identified β-lactam antibiotics or glutamate derivatives or analogs include metal salts, *e.g.* aluminum, alkali metal salts such as sodium or potassium, alkaline earth metal salts such as calcium or magnesium, and ammonium or substituted ammonium salts, for example those with lower alkylamines such as triethylamine, hydroxy-lower alkylamines such as 2-hydroxyethylamine, bis-(2-hydroxyethyl)amine or tris-(2-hydroxyethyl)amine, cycloalkylamines such as dicyclohexylamine, or with procaine, dibenzylamine, N,N-dibenzylethylenediamine, 1-ephenamine, N-methylmorpholine, ~~-ethylpiperidine~~N-ethylpiperidine, N-benzyl-β-phenethylamine, dehydroabietylamine, ~~N,N'-bisdehydro-abietylamine~~N,N'-bisdehydro-abietylamine, ethylenediamine, or ~~bases of te~~ bases of the pyridine type such as pyridine, collidine or quinoline, or other amines which have been used to form salts with known penicillins and cephalosporins. Other useful salts include the lithium salt and silver salt. Salts within compounds of formula (I), may be prepared by salt exchange in conventional manner.

8. Please amend the paragraphs beginning on page 69, line 5 and ending on line 15, as follows:

These data indicate that the antiaggressive effect of the beta-lactam antibiotic Mox may be extended to include the beta-lactam ampicillin. ~~Off all of the~~Of all of the antibiotic tested, Mox has the greatest penetrability into the CNS. Patents given 2.0 g of Mox IV show cerebrospinal fluid levels of drug around 30 μg/ml. The ratio of CSF to serum levels of Mox is ca. 15-20%. It is estimated that the serum concentration of Mox in 140 g hamster

given an IP injection of 14 μg of drug is 0.1 ng/ml. This would be reflected by a CSF concentration of 15 ng/ml or brain levels of Mox approximating 30 nM. These levels would certainly be in range to interact effectively with neuropeptide receptors most of which have binding affinities in the nanomolar range. Interaction with the classical neurotransmitters would be less likely because these receptors have Kd's in the micro and millimolar range.

9. Please amend the paragraphs beginning on page 90, line 1 and ending on line 11, as follows:

Active site I:
35 AA's ~~upstream~~downstream from N-terminus: STTK (SEQ ID NO:1)

Active site II:
57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif: SGC, SGN, or SAN

Active site III:
111 AA's ~~upstream~~downstream from SGC motif: KTG

Active site IV:
41 AA's ~~upstream~~downstream from SGC motif: ENKD (SEQ ID NO:2)

10. Please amend the paragraphs beginning on page 90, line 25 and ending on page 91, line 3, as follows:

Active site I:
Beta-lactamase: 35 AA's ~~upstream~~downstream from N-terminus: STTK (SEQ ID NO:1)
NAALADase: 38 AA's ~~upstream~~downstream from N-terminus: STQK (SEQ ID NO:3)

Active site II:
Beta-lactamase: 57 AA's ~~upstream~~downstream from STTK (SEQ ID NO:1) motif: SGC, SGN, or SAN
NAALADase: 59 AA's ~~upstream~~downstream from STQK (SEQ ID NO:3) motif: SFG

Active site III:
Beta-lactamase: 111 AA's ~~upstream~~downstream from SGC motif: KTG
NAALADase: 110 AA's ~~upstream~~downstream from SFG motif: KLG

Active site IV:
Beta-lactamase: 41 AA's ~~upstream~~downstream from SGC motif: ENKD (SEQ ID NO:2)

NAALADase: 41 AA's ~~upstream~~downstream from SFG motif: ERGV (SEQ ID NO:4)

Amendments to the Specification under 37 C.F.R. § 1.121(B)(1)

Please amend the abstract as follows:

Abstract of the Disclosure

Administration of β-Lactam compounds, including β-lactam antibiotics and β-lactamase inhibitors provides ~~of inhibitors of certain bacterial peptidase have been found to provide~~ significant neurotropic effects in warm-blooded vertebrates evidenced *inter alia* by anxiolytic and anti-aggressive behavior modification and enhanced cognition ~~believed to be mediated by inhibition of neurogenic NAALADase and related enzyme activity. β-Lactam antibiotics and β-lactamase inhibitors have been found to exhibit potent NAALADase inhibition, and those compounds with blood brain barrier transport are effective inhibitors of neurogenic NAALADase with significant neuro-therapeutic effects. β-Lactam compounds are useful for treatment of numerous disease states associated with glutamate abnormalities~~. Therapeutic methods for using such compounds and their pharmaceutical formulations are described.